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PCT / SE 2004 / 000534

REC'D 29 APR 2004
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The application was originally filed in English.

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(21) *Patentansökningsnummer* *0301009-7*
Patent application number

(86) *Ingivningsdatum* *2003-04-07*
Date of filing

Stockholm, 2004-04-19

För Patent- och registreringsverket
For the Patent- and Registration Office

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Avgift
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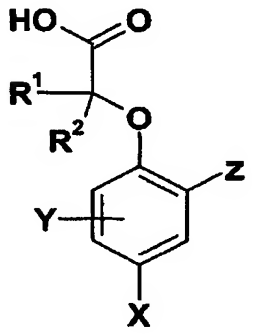
NOVEL COMPOUNDS

The present invention relates to substituted phenoxyacetic acids as useful pharmaceutical compounds for treating respiratory disorders, pharmaceutical compositions containing them, and processes for their preparation.

EPA 1 170 594 discloses methods for the identification of compounds useful for the treatment of disease states mediated by prostaglandin D2, a ligand for orphan receptor CRTH2. GB 1356834 discloses a series of compounds said to possess anti-inflammatory, analgesic and antipyretic activity. It has been found that certain phenoxyacetic acids are active at the CRTH2 receptor, and as a consequence are expected to be potentially useful for the treatment of various respiratory diseases, including asthma and COPD.

In a first aspect the invention therefore provides a compound of formula (I) or a pharmaceutically acceptable salt thereof:



(I)

in which

X is C_{1-6}alkyl, OR^6 or OR^{17}

Y is selected from hydrogen, halogen, CN, nitro, SO_2R^3, OR^4, SR^4, SOR^3, $SO_2NR^4R^5$, $CONR^4R^5$, NR^4R^5, $NR^6SO_2R^3$, $NR^6CO_2R^6$, NR^6COR^3, C_2-C_6 alkenyl, C_2-C_6 alkynyl, C_3-C_7 cycloalkyl or C_{1-6}alkyl, the latter four groups being optionally substituted by one or more substituents independently selected from halogen, OR^6 and NR^6R^7, $S(O)_nR^6$ where n is 0, 1 or 2;

Z is aryl or a ring A, where A is a six membered heterocyclic aromatic ring containing one or more nitrogen atoms or may be a 6,6 or 6,5 fused bicycle containing one or more O, N,

S atoms, the aryl or A rings all being optionally substituted by one or more substituents independently selected from from hydrogen, halogen, CN, OH, SH, nitro, CO_2R^6, SO_2R^9, OR^9, SR^9, SOR^9, $SO_2NR^{10}R^{11}$, $CONR^{10}R^{11}$, $NR^{10}R^{11}$, $NHSO_2R^9$, $NR^9SO_2R^9$, $NR^6CO_2R^6$, $NHCOR^9$, NR^9COR^9, aryl, heteroaryl, C_2-C_6 alkenyl, C_2-C_6 alkynyl, C_3-C_7 cycloalkyl or C_{1-6}alkyl, the latter four groups being optionally substituted by one or more substituents independently selected from halogen, C_3-C_7 cycloalkyl, OR^6, NR^6R^7, $S(O)_nR^6$ (where n is 0, 1 or 2), $CONR^6R^7$, NR^6COR^7, $SO_2NR^6R^7$ and $NR^6SO_2R^7$.

R^1 and R^2 independently represent a hydrogen atom, C_2-C_6 alkenyl, C_2-C_6 alkynyl, C_3-C_7 cycloalkyl or a C_{1-6}alkyl group, the latter four groups being optionally substituted by one or more substituents independently selected from halogen, C_3-C_7 cycloalkyl, NR^6R^7, OR^6, $S(O)_nR^6$ (where n is 0, 1 or 2);

or

R^1 and R^2 together can form a 3-8 membered ring optionally containing one or more atoms selected from O, S, NR^6 and itself optionally substituted by one or more C_1-C_3 alkyl or halogen;

R^3 represents C_3-C_7 cycloalkyl or C_{1-6}alkyl which may be optionally substituted by one or more substituents independently selected from halogen, C_3-C_7 cycloalkyl, OR^6 and NR^6R^7, $S(O)_nR^6$ (where n = 0,1 or 2), $CONR^6R^7$, NR^6COR^7,$SO_2NR^6R^7$ and $NR^6SO_2R^7$;

R^4 and R^5 independently represent hydrogen, C_3-C_7 cycloalkyl or C_{1-6}alkyl, the latter two groups being optionally substituted by one or more substituents independently selected from halogen, C_3-C_7 cycloalkyl, OR^6 and NR^6R^7, $S(O)_nR^6$ (where n = 0,1 or 2), $CONR^6R^7$, NR^6COR^7,$SO_2NR^6R^7$ and $NR^6SO_2R^7$;

or

R^4 and R^5 together with the nitrogen atom to which they are attached can form a 3-8 membered saturated heterocylic ring optionally containing one or more atoms selected from O, $S(O)_n$ (where n = 0,1 or 2), NR^8, and itself optionally substituted by halogen or C_1-$_3$ alkyl;

R^6 and R^7 independently represents a hydrogen atom or C_1-C_6 alkyl;

R^8 is hydrogen, C_{1-4} alkyl, -COC_1-C_4 alkyl, CO_2C_1-C_4alkyl or $CONR^6C_1$-C_4alkyl;

R^9 represents aryl, heteroaryl, C_3-C_7 cycloalkyl or C_{1-6}alkyl, the latter two groups may be optionally substituted by one or more substituents independently selected from halogen, C_3-C_7 cycloalkyl, aryl, heteroaryl OR^6 and NR^6R^7, $S(O)_nR^6$ (where n = 0, 1 or 2), $CONR^6R^7$, NR^6COR^7, $SO_2NR^6R^7$ and $NR^6SO_2R^7$;

R^{10} and R^{11} independently represent aryl or heteroaryl, hydrogen, C_3-C_7 cycloalkyl or C_{1-6}alkyl, the latter two groups being optionally substituted by one or more substituents independently selected from halogen, C_3-C_7 cycloalkyl, aryl, heteroaryl, OR^6 and NR^6R^7, $S(O)_nR^6$ (where n = 0, 1 or 2), $CONR^6R^7$, NR^6COR^7, $SO_2NR^6R^7$ and $NR^6SO_2R^7$;

or

R^{10} and R^{11} together with the nitrogen atom to which they are attached can form a 3-8 membered saturated heterocylic ring optionally containing one or more atoms selected from O, $S(O)_n$ (where n = 0, 1 or 2), NR^8, and itself optionally substituted by halogen or C_1-C_3 alkyl.

R^{17} is C_{1-6} alkyl which is substituted by one or more halogen atoms;

Examples of aryl include phenyl and naphthyl.

Heteroaryl is defined as a 5-7 member aromatic ring or can be 6,6- or 6,5-fused bicyclic ring optionally containing one or more heteroatoms selected from N, S, O. Examples include pyridine, pyrimidine, thiazole, oxazole, pyrazole, imidazole, furan, isoxazole, pyrrole, isothiazole and azulene, naphthyl, indene, quinoline, isoquinoline, indole, indolizine, benzo[b]furan, benzo[b]thiophene, 1H-indazole, benzimidazole, benzthiazole, benzoxazole, purine, 4H-quinolizine, cinnoline, phthalazine, quinazoline, quinoxaline, 1,8-naphthyridine, pteridine and quinolone.

Aryl or heteroaryl groups can be optionally substituted by one or more substituents independently selected from from hydrogen, halogen, CN, OH, SH, nitro, CO_2R^6, SO_2R^9, OR^9, SR^9, SOR^9, $SO_2NR^{10}R^{11}$, $CONR^{10}R^{11}$, $NR^{10}R^{11}$, $NHSO_2R^9$, $NR^9SO_2R^9$, $NR^6CO_2R^6$, $NHCOR^9$, NR^9COR^9, aryl, heteroaryl, C_2-C_6 alkenyl, C_2-C_6 alkynyl, C_3-C_7 cycloalkyl or

C_{1-6}alkyl, the latter four groups being optionally substituted by one or more substituents independently selected from halogen, C_3-C_7 cycloalkyl , OR^6, NR^6R^7, $S(O)_nR^6$ (where n is 0, 1 or 2), $CONR^6R^7$, NR^6COR^7, $SO_2NR^6R^7$ and $NR^6SO_2R^7$.

The group A is a six membered heterocyclic ring containing one or more nitrogen atoms or may be a 6,6 or 6,5 fused bicycle containing one or more O, N, S atoms. Examples of suitable rings include pyridine, pyrimidine, pyrazine, pyridazine, indole, quinoline, isoquinoline, benzimidazole, benzthiazole, benzofuran, benzoxazole, benzthiophene, phthalazine, quinazoline.

In the context of the present specification, unless otherwise indicated, an alkyl or alkenyl group or an alkyl or alkenyl moiety in a substituent group may be linear or branched.

Heterocyclic rings as defined for R^4, R^5 and R^{10}, R^{11} means saturated heterocycles, examples include morpholine, azetidine, pyrrolidine, piperidine and piperazine.

Preferably X is C_{1-4}alkyl or C_{1-4}alkoxy, more preferably methyl, ethyl or methoxy.

Preferably Y is hydrogen.

Preferably Z is phenyl optionally substituted by SO_2R^9, more preferably Z is phenyl optionally substituted by SO_2Me or SO_2Et.

Preferably R^1 and R^2 are independently hydrogen or C_{1-3} alkyl.

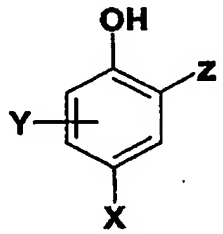
Preferred compounds of the invention include:
[(5-Methylbiphenyl-2-yl)oxy]acetic acid,
{[5-Ethyl-4'-(methylsulfonyl)biphenyl-2-yl]oxy}acetic acid
{[4'-(Ethylsulfonyl)-5-methoxybiphenyl-2-yl]oxy}acetic acid
and pharmaceutically acceptable salts and solvates thereof.

Certain compounds of formula (I) are capable of existing in stereoisomeric forms. It will be understood that the invention encompasses all geometric and optical isomers of the compounds of formula (I) and mixtures thereof including racemates. Tautomers and mixtures thereof also form an aspect of the present invention.

The compound of formula (I) above may be converted to a pharmaceutically acceptable salt or solvate thereof, preferably a basic addition salt such as sodium, potassium, calcium, aluminium, lithium, magnesium, zinc, benzathine, chloroprocaine, choline, diethanolamine, ethanolamine, ethyldiamine, meglumine, tromethamine or procaine, or an acid addition salt such as a hydrochloride, hydrobromide, phosphate, acetate, fumarate, maleate, tartrate, citrate, oxalate, methanesulphonate or *p*-toluenesulphonate.

It will be appreciated by those skilled in the art that in the processes of the present invention certain functional groups in the starting reagents or intermediate compound may need to be protected by protecting groups. Thus, the preparation of the compound of formula (I) may involve, at an appropriate stage, the removal of one or more protecting groups. The protection and deprotection of functional groups is fully described in 'Protective Groups in Organic Chemistry', edited by J. W. F. McOmie, Plenum Press (1973), and 'Protective Groups in Organic Synthesis', 3rd edition, T. W. Greene & P. G. M. Wuts, Wiley–Interscience (1999).

Compounds of formula (I) can be prepared by reaction of a compound of formula (II):



(II)

in which X, Y and Z are as defined in formula (I) or are protected derivatives thereof, with a compound of formula (III):

$L\text{-}CR^1R^2CO_2R^{12}$ (III)

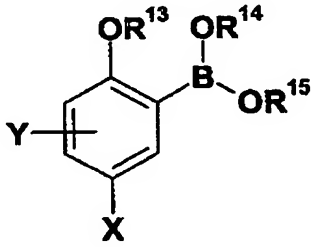
Where R^1 and R^2 are as defined in formula (I) or are protected derivatives thereof, R^{12} is H or C_1-C_{10} alkyl group and L is a leaving group, and optionally thereafter in any order:

- removing any protecting group
- hydrolysing the ester group R^{12} to the corresponding acid
- oxidation of sulphides to sulphoxides or sulphones
- forming a pharmaceutically acceptable salt.

The reaction can be carried out in a suitable solvent such as DMF using a base such as potassium carbonate or the like. Suitable groups R^{12} include C_{1-6} alkyl groups such as methyl, ethyl or tert-butyl. Suitable L is a leaving group such as halo, in particular chlorine or bromine.

Hydrolysis of the ester group R^{12} can be carried out using routine procedures, for example treatment of methyl and ethyl esters with aqueous sodium hydroxide, and treatment of tert-butyl esters with acids such as trifluoroacetic acid.

Compounds of formula (II) can be prepared by reaction of a compound of formula (IV) with a compound of formula (V) *via* a Suzuki coupling reaction followed by deprotection of R^{13} when R^{13} is not equal to H :



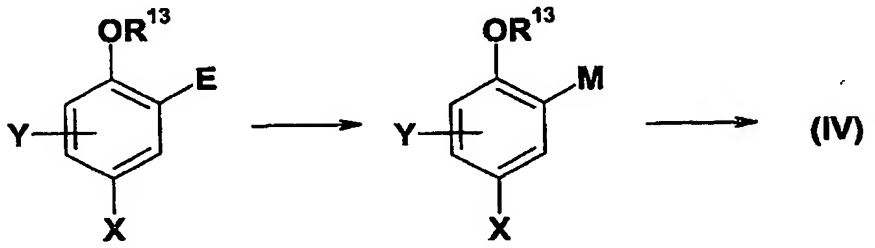
(IV)

(V)

in which X, Y and Z are as defined in formula (I) or are protected derivatives thereof, R^{13} is H or a suitable protecting group, for example benzyl, L^1 is iodide, bromide, chloride or triflate and R^{14} and R^{15} are H or C_1-C_6 alkyl groups or R^{14} and R^{15} together can form a 5 or 6 membered ring optionally substituted by one or more C_1-C_3 alkyl.

The reaction can be carried out in a suitable solvent such as dioxane using a palladium catalyst such as [1,1-bis(diphenylphosphino)ferrocene]dichloropalladium and a base such as cesium fluoride, preferably at elevated temperatures.

Compounds of formula (IV) can be prepared from a compound of formula (VI) by formation of an organometallic (VII) followed by reaction with a borate ester, as outlined in Scheme I.

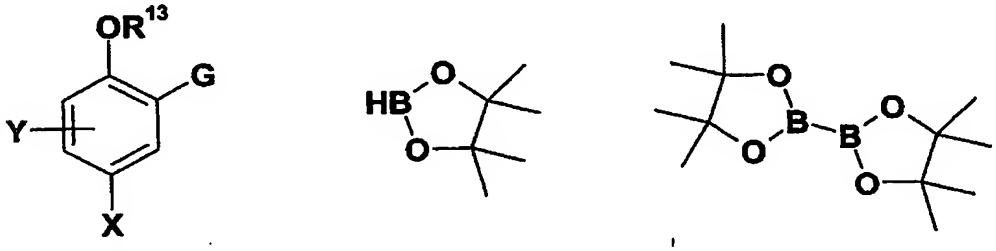


(VI) (VII)

Scheme I

in which X, Y are as defined in formula (I) or are protected derivatives thereof, R^{13} is as defined in formula (IV), E is hydrogen or halogen and M is a metal such as Na or Li. For example when R^{13} is benzyl and E is bromine, butyl lithium can be used to form the intermediate (VII) where M = Li. The reaction is performed at –78°C in diethylether, then quenched with a borate ester such as trimethylborate.

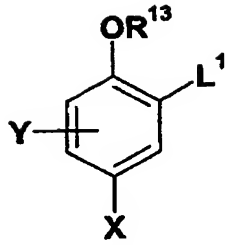
Compounds of formula (IV) may also be prepared by a palladium catalysed coupling of compounds of formula (VIII) with a suitable boronic ester, for example (IX) or (X).



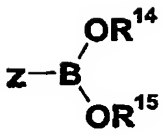
(VIII) (IX) (X)

in which X, Y and R^{13} are as defined above and G is halogen or triflate

Compounds of formula (II) may also be prepared by reaction of a compound of formula (XI) with a compound of formula (XII) using Suzuki coupling methodology.



(XI)

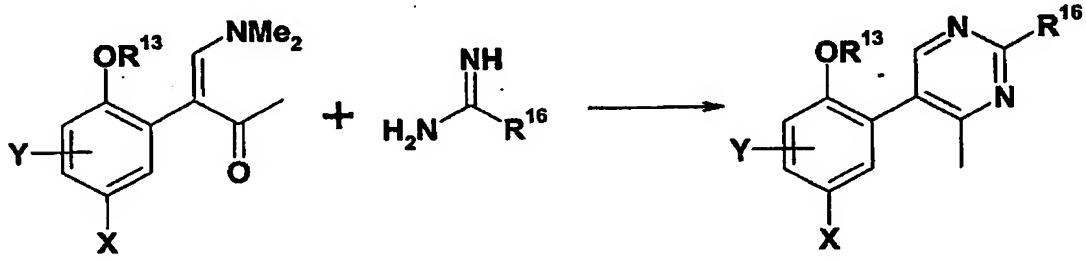


(XII)

in which X, Y, Z, R^{13}, L^1, R^{14} and R^{15} are as defined above and compounds of formula (XI) and (XII) can be made using the same methodology as above.

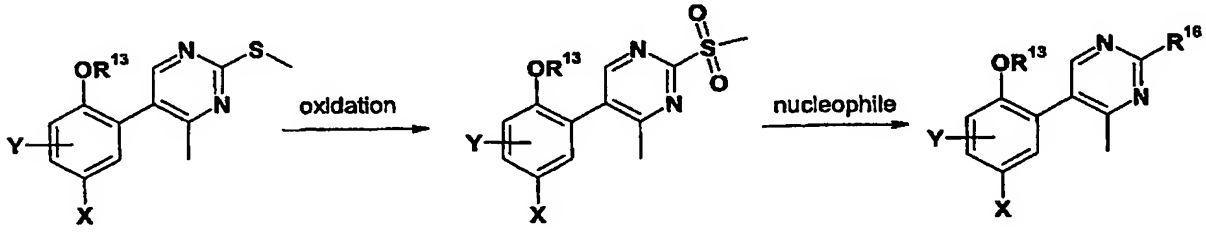
Compounds of formula (II), where Z=heteroaryl may also be prepared by ring synthesis, for example a compound of formula (XIII) may be formed by reaction of a compound of formula (XIV) with a compound of formula (XV).

X, Y and R^{13} are as defined above and R^{16} is as defined as a substituent on Z as defined in formula (I) or are protected derivatives thereof. The reaction can be carried out in a solvent such as ethanol under reflux, and a base such as sodium ethoxide can be used if compound of formula (XV) is a salt



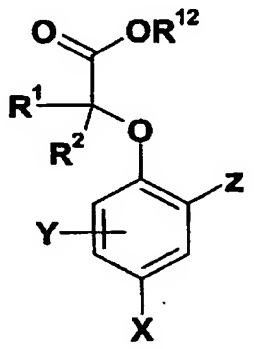
(XIV) (XV) (XIII)

When R^{16} is a group S-alkyl, this may be further elaborated by oxidation to the sulfoxide or sulphone using an oxidizing agent such as mcpba in DCM at RT. This may then be displaced with an appropriate nucleophile as defined for Z in formula 1. Scheme 2;

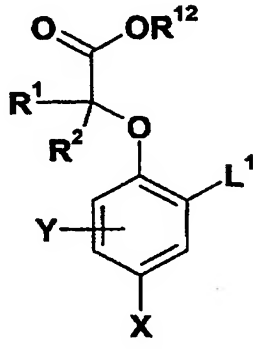


Scheme 2

The sequence of the steps above may be changed, for example a compound of formula (XVI) may be formed by the reaction of a compound of formula (XVII) with a compound of formula (XII) using a Suzuki coupling.



(XVI)



(XVII)

In a further aspect, the present invention provides the use of a compound of formula (I), a prodrug, pharmaceutically acceptable salt or solvate thereof for use in therapy.

The compounds of formula (I) have activity as pharmaceuticals, in particular as modulators of CRTh2 receptor activity, and may be used in the treatment (therapeutic or prophylactic) of conditions/diseases in human and non-human animals which are exacerbated or caused by excessive or unregulated production of PGD_2 and its metabolites. Examples of such conditions/diseases include:

(1) **(the respiratory tract)** obstructive airways diseases including: asthma (such as bronchial, allergic, intrinsic, extrinsic and dust asthma particularly chronic or inveterate asthma (e.g. late asthma and airways hyper-responsiveness)); chronic obstructive pulmonary disease (COPD)(such as irreversible COPD); bronchitis (including eosinophilic bronchitis); acute, allergic, atrophic rhinitis or chronic rhinitis (such as rhinitis caseosa, hypertrophic rhinitis, rhinitis purulenta, rhinitis sicca), rhinitis medicamentosa, membranous rhinitis (including croupous, fibrinous and pseudomembranous rhinitis), scrofoulous rhinitis, **perennial allergic rhinitis,** easonal rhinitis (including rhinitis nervosa (hay fever) and vasomotor rhinitis); nasal polyposis; sarcoidosis; farmer's lung and related diseases; fibroid lung; idiopathic interstitial pneumonia; cystic

fibrosis; antitussive activity; treatment of chronic cough associated with inflammation or iatrogenic induced ;

(2) **(bone and joints)** arthrides including rheumatic, infectious, autoimmune, seronegative, spondyloarthropathies (such as ankylosing spondylitis, psoriatic arthritis and Reiter's disease), Behcet's disease, Sjogren's syndrome and systemic sclerosis;

(3) **(skin and eyes)** psoriasis, atopical dermatitis, contact dermatitis, other eczmatous dermitides, seborrhoetic dermatitis, Lichen planus, Pemphigus, bullous Pemphigus, Epidermolysis bullosa, urticaria, angiodermas, vasculitides, erythemas, cutaneous eosinophilias, chronic skin ulcers, uveitis, Alopecia areatacorneal ulcer and vernal conjunctivitis;

(4) **(gastrointestinal tract)** Coeliac disease, proctitis, eosinopilic gastro-enteritis, mastocytosis, Crohn's disease, ulcerative colitis, irritable bowel disease; food-related allergies which have effects remote from the gut, (such as migraine, rhinitis and eczema);

(5) **(central and peripheral nervous system)** Neurodegenerative diseases and dementia disorders (such as Alzheimer's disease, amyotrophic lateral sclerosis and other motor neuron diseases, Creutzfeldt-Jacob's disease and other prion diseases, HIV encephalopathy (AIDS dementia complex), Huntington's disease, frontotemporal dementia, Lewy body dementia and vascular dementia), polyneuropathies (such as Guillain-Barré syndrome, chronic inflammatory demyelinating polyradiculoneuropathy, multifocal motor neuropathy), plexopathies, CNS demyelination (such as multiple sclerosis, acute disseminated/haemorrhagic encephalomyelitis, and subacute sclerosing panencephalitis), neuromuscular disorders (such as myasthenia gravis and Lambert-Eaton syndrome), spinal diorders (such as tropical spastic paraparesis, and stiff-man syndrome), paraneoplastic syndromes (such as cerebellar degeneration and encephalomyelitis), CNS trauma, migraine and stroke.

(6) **(other tissues and systemic disease)** atherosclerosis, acquired Immunodeficiency Syndrome (AIDS), lupus erythematosus; systemic lupus, erythematosus; Hashimoto's thyroiditis, type I diabetes, nephrotic syndrome,

eosinophilia fascitis, hyper IgE syndrome, lepromatous leprosy, idiopathic thrombocytopenia pupura; post-operative adhesions, sepsis and ischemic/reperfusion injury in the heart, brain, **peripheral limbs hepatitis (alcoholic, steatohepatitis and chronic viral) , glomerulonephritis, renal impairment, chronic renal failure and other organs**

(7) **(allograft rejection)** acute and chronic following, for example, transplantation of kidney, heart, liver, lung, bone marrow, skin and cornea; and chronic graft versus host disease;

(8) Diseases associated with raised levels of PGD_2 or its metabolites.

Thus, the present invention provides a compound of formula (I), or a pharmaceutically-acceptable salt or solvate thereof, as hereinbefore defined for use in therapy.

Preferably the compounds of the invention are used to treat diseases in which the chemokine receptor belongs to the CRTh2 receptor subfamily.

Particular conditions which can be treated with the compounds of the invention are asthma, rhinitis and other diseases in which raised levels of PGD_2 or its metabolites. It is preferred that the compounds of the invention are used to treat asthma.

In a further aspect, the present invention provides the use of a compound of formula (I), or a pharmaceutically acceptable salt or solvate thereof, as hereinbefore defined in the manufacture of a medicament for use in therapy.

In a further aspect, the present invention provides the use of a compound or formula (I), or a pharmaceutically acceptable salt or solvate thereof, as hereinbefore defined in the manufacture of a medicament for use in therapy in combination with drugs used to treat asthma and rhinitis (such as inhaled and oral steroids, inhaled β2-receptor agonists and oral leukotriene receptor antagonists).

In a still further aspect, the present invention provides the use of a compound of formula (I), or a pharmaceutically acceptable salt or solvate thereof, as hereinbefore defined in the manufacture of a medicament for the treatment of human diseases or conditions in which modulation of CRTh2 receptor activity is beneficial.

In the context of the present specification, the term "therapy" also includes "prophylaxis" unless there are specific indications to the contrary. The terms "therapeutic" and "therapeutically" should be construed accordingly.

The invention still further provides a method of treating diseases mediated by PGD2 or its metabolites wherein the prostanoid binds to its receptor (especially CRTh2) receptor, which comprises administering to a patient a therapeutically effective amount of a compound of formula (I), or a pharmaceutically acceptable salt, solvate or prodrug thereof, as hereinbefore defined.

The invention also provides a method of treating an inflammatory disease, especially psoriasis, in a patient suffering from, or at risk of, said disease, which comprises administering to the patient a therapeutically effective amount of a compound of formula (I), or a pharmaceutically acceptable salt or solvate thereof, as hereinbefore defined.

For the above-mentioned therapeutic uses the dosage administered will, of course, vary with the compound employed, the mode of administration, the treatment desired and the disorder indicated.

For the above-mentioned therapeutic uses the dosage administered will, of course, vary with the compound employed, the mode of administration, the treatment desired and the disorder indicated.

The compound of formula (I), prodrugs and pharmaceutically acceptable salts and solvates thereof may be used on their own but will generally be administered in the form of a pharmaceutical composition in which the formula (I) compound/salt/solvate (active ingredient) is in association with a pharmaceutically acceptable adjuvant, diluent or carrier. Depending on the mode of administration, the pharmaceutical composition will preferably comprise from 0.05 to 99 %w (per cent by weight), more preferably from 0.05 to 80 %w, still more preferably from 0.10 to 70 %w, and even more preferably from 0.10 to 50 %w, of active ingredient, all percentages by weight being based on total composition.

The present invention also provides a pharmaceutical composition comprising a compound of formula (I), or a pharmaceutically acceptable salt or solvate thereof, as herein before defined, in association with a pharmaceutically acceptable adjuvant, diluent or carrier.

The pharmaceutical compositions may be administered topically (e.g. to the lung and/or airways or to the skin) in the form of solutions, suspensions, heptafluoroalkane aerosols and dry powder formulations; or systemically, e.g. by oral administration in the form of tablets, capsules, syrups, powders or granules, or by parenteral administration in the form of solutions or suspensions, or by subcutaneous administration or by rectal administration in the form of suppositories or transdermally. Preferably the compound of the invention is administered orally.

The invention will now be illustrated by the following examples in which, unless stated otherwise:

(i) when given, ^{1}H NMR data is quoted in the form of delta values for major diagnostic protons, given in parts per million (ppm) relative to tetramethylsilane (TMS) as an internal standard;

(ii) mass spectra (MS): generally only ions which indicate the parent mass are reported, and unless otherwise stated the mass ion quoted is the positive mass ion - $(M+H)^+$;

(iii) the title compounds of the examples and methods were named using the ACD/name batch (version 6.0) from Advanced Chemical Development Inc, Canada;

(iv) unless stated otherwise, reverse phase HPLC was conducted using a Symmetry, NovaPak or Ex-Terra reverse phase silica column;

(v) solvents were dried with $MgSO_4$ or Na_2SO_4

(vi) the following abbreviations are used:

EtOAc	Ethylacetate
DCM	Dichloromethane
NMP	N-methylpyrrolidine
DMF	N,N-dimethylformamide
THF	tetrahydrofuran
mcpba	3-chloroperoxybenzoic acid (Aldrich 77% max)
$Pd(dppf)Cl_2$	[1,1'-Bis(diphenylphosphino)ferrocene]dichloropalladium(II), complex with dichloromethane
RT	room temperature

Example 1

[(5-Methylbiphenyl-2-yl)oxy]acetic acid

(i) tert-Butyl (2-bromo-4-nitrophenoxy)acetate

tert-Butyl bromoacetate (3.06ml) was added to a stirred mixture of 2-bromo-4-nitrophenol (4g) and potassium carbonate (2.62g) in DMF (40ml) at RT. After 18h the reaction was partitioned between diethylether and water, the organics separated, dried and evaporated under reduced pressure. The residue was triturated with iso-hexane and filtered. Yield 5.6g

^{1}H NMR $CDCl_3$: δ 8.49 (1H, d) ; 8.21-8.16 (1H, m) ; 6.82 (1H, d) ; 4.71 (2H, s) ; 1.49 (9H, s)

(ii) tert-Butyl [(5-nitrobiphenyl-2-yl)oxy]acetate

A mixture of the product from step (i) (5.6g), benzeneboronic acid (2.04g), cesium fluoride (5.1g) and $Pd(dppf)Cl_2$ (0.6g) in dioxane (60ml) was heated under reflux for 4h. After cooling the mixture was partitioned between diethylether and water. The organics were separated, dried and evaporated under reduced pressure.

MS: APCI (+ve): 272 (M+1 - ^{t}Bu)

(iii) tert-Butyl [(5-aminobiphenyl-2-yl)oxy]acetate

Iron powder (5g) was added to a solution of the product from step (ii) in acetic acid (100ml) and stirred at RT for 16h. The mixture was filtered through celite and evaporated under reduced pressure. The resulting oil was made basic with aqueous sodium hydroxide solution then extracted with EtOAc. The organics were dried, evaporated under reduced pressure and the residue purified by chromatography on silica eluting with 8:1 DCM/EtOAc. Yield 3.74g

MS: APCI (-ve): 272 (M-1-^{t}Bu)

(iv) tert-Butyl [(5-bromobiphenyl-2-yl)oxy]acetate

Copper (II) bromide (2.67g) was added to a mixture of the product from step (iii) (3g) and isoamylnitrite (2ml) in acetonitrile (40ml) and heated at 65°C for 2h. The solvent was evaporated under reduced pressure and the residue purified by chromatography on silica eluting with 5:1 isohexane/diethylether. Yield 2.33g

MS: APCI (-ve): 306/7 (M-1-^{t}Bu)

(v) tert-Butyl [(5-methylbiphenyl-2-yl)oxy]acetate

A mixture of the product from step (iv) (0.5g), methylzinc chloride (3.44ml, 2M in THF) and $Pd(dppf)Cl_2$ (0.1g) in THF (10ml) was heated at 90°C for 4h. After cooling the mixture was partitioned between diethylether and water, the organics separated, dried and evaporated under reduced pressure. The residue was purified by chromatography on silica eluting with 4:1 isohexane/diethylether. Yield 0.43g

MS: APCI (-ve): 241 (M-1-^{t}Bu)

(vi) [(5-Methylbiphenyl-2-yl)oxy]acetic acid

A solution of the product from step (v) (0.43g) and trifluoroacetic acid (10ml) in DCM (10ml) was stirred at RT for 1h then evaporated under reduced pressure. The residue was purified by chromatography on silica eluting with 1:1 DCM/EtOAc + 1% AcOH then by RPHPLC. Yield 0.03g

^{1}H NMR DMSO-d6: δ 7.56-6.85 (8H, m) ; 4.64 (2H, s) ; 2.27 (3H, s)
MS: APCI (-ve): 241 (M-1)

Example 2

{[5-Ethyl-4'-(methylsulfonyl)biphenyl-2-yl]oxy}acetic acid

(i) tert-Butyl (4-ethyl-2-iodophenoxy)acetate

Sodium iodide (4.41g) then chloramine-T (8.29g) was added to a stirred solution of 4-ethylphenol (3g) at 0°C then allowed to warm to RT. After 1h the mixture was diluted with 2M hydrochloric acid and extracted with diethylether. The organic layer was washed with aqueous sodium thiosulphate solution, dried and evaporated under reduced pressure. The residue was dissolved in DMF (30ml) then tert-butyl bromoacetate (3.9ml) and potassium carbonate (3.31g) added and stirred at RT overnight. The mixture was partitioned between water and diethylether, the organics dried and evaporated under reduced pressure. The residue was purified by chromatography on silica eluting with 20% diethylether/isohexane. Yield 8.6g

MS: APCI (-ve): 305 (M-1-^{t}Bu)

(ii) tert-Butyl {[5-ethyl-4'-(methylthio)biphenyl-2-yl]oxy}acetate

The subtitle compound was prepared by the method of example 1 step (ii) using the product from step (i) and 4-(methylthio)benzeneboronic acid. Yield 1.2g

MS: APCI (-ve): 301 (M-1-^{t}Bu)

(iii) {[5-Ethyl-4'-(methylsulfonyl)biphenyl-2-yl]oxy}acetic acid

Mcpba (1.44g) was added to a stirred solution of the product from step (ii) (1.2g) in DCM (10ml) at RT. After 16h, the mixture was partitioned between DCM and aqueous sodium metabisulphite solution, the organics separated, washed with aqueous sodium hydrogencarbonate solution, water, dried and evaporated under reduced pressure. The residue was dissolved in trifluoroacetic acid (10ml) and DCM (10ml), stirred at RT for 2h then evaporated under reduced pressure. The residue was purified by RPHPLC. Yield 0.035g

^{1}H NMR DMSO-d6: δ 7.95-6.94 (7H, m) ; 4.71 (2H, s) ; 3.25 (3H, s) ; 2.62-2.57 (2H, q) ; 1.20-1.17 (3H, t)

MS: APCI (-ve): 333 (M-1)

Example 3

{[4'-(Ethylsulfonyl)-5-methoxybiphenyl-2-yl]oxy}acetic acid

(i) tert-Butyl (2-bromo-4-methoxyphenoxy)acetate

The subtitle compound was prepared by the method of example 1 step (i) using 2-bromo-4-methoxyphenol. Yield 1.9g

MS: APCI (-ve): 251 (M-1-^{t}Bu)

(ii) tert-Butyl {[4'-(ethylthio)-5-methoxybiphenyl-2-yl]oxy}acetate

The subtitle compound was prepared by the method of example 1 step (ii) using the product from step (i) and 4-(ethylthio)benzeneboronic acid. Yield 1.15g

MS: APCI (-ve): 317 (M-1-^{t}Bu)

(iii) {[4'-(Ethylsulfonyl)-5-methoxybiphenyl-2-yl]oxy}acetic acid

The title compound was prepared by the method of example 2 step (iii) using the product from step (ii). Yield 0.12g

^{1}H NMR DMSO-d6: δ 7.92-7.85 (4H, m) ; 7.01-6.92 (3H, m) ; 4.68-4.66 (2H, s) ; 3.76 (3H, s) ; 3.37-3.29 (2H, m) ; 1.17-1.12 (3H, t)

MS: APCI (-ve): 349 (M-1)

Pharmacological Data

Ligand Binding Assay

[^{3}H]PGD_2 was purchased from Perkin Elmer Life Sciences with a specific activity of 100-210Ci/mmol. All other chemicals were of analytical grade.

HEK cells expressing rhCRTh2 / Gα16 were routinely maintained in DMEM containing 10% Foetal Bovine Serum (HyClone), 1mg/ml geneticin, 2mM L-glutamine and 1% non-essential amino acids. For the preparation of membranes, the adherent transfected HEKcells were grown to confluence in two layer tissue culture factories (Fisher, catalogue number TKT-170-070E). Maximal levels of receptor expression were induced by addition of 500mM sodium butyrate for the last 18 hours of culture. The adherent cells were washed once with phosphate buffered saline (PBS, 50ml per cell factory) and detached by the addition of 50ml per cell factory of ice-cold membrane homogenisation buffer [20mM HEPES (pH 7.4), 0.1mM dithiothreitol, 1mM EDTA, 0.1mM phenyl methyl sulphonyl fluoride and 100µg/ml bacitracin]. Cells were pelleted by centrifugation at 220xg for 10 minutes at 4°C, re-suspended in half the original volume of fresh membrane homogenisation buffer and disrupted using a Polytron homogeniser for 2 x 20 second bursts keeping the tube in ice at all times. Unbroken cells were removed by centrifugation at 220xg for 10 minutes at 4°C and the membrane fraction pelleted by centrifugation at 90000xg for 30 minutes at 4°C. The final pellet was re-suspended in 4 ml of membrane homogenisation buffer per cell factory used and the protein content determined. Membranes were stored at -80°C in suitable aliquots.

All assays were performed in Corning clear bottomed, white 96-well NBS plates (Fisher). Prior to assay, the HEK cells membranes containing CRTh2 were coated onto SPA PVT WGA beads (Amersham). For coating membranes were incubated with beads at typically 25µg membrane protein per mg beads at 4°C with constant agitation overnight. (The optimum coating concentrations were determined for each batch of membranes) The beads were pelleted by centrifugation (800xg for 7minutes at 4°C), washed once with assay buffer (50mM HEPES pH 7.4 containing 5mM magnesium chloride) and finally re-suspended in assay buffer at a bead concentration of 10mg/ml.

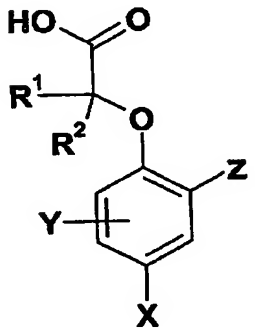
Each assay contained 20µl of 6.25nM [^{3}H]PGD_2, 20µl membrane saturated SPA beads both in assay buffer and 10µl of compound solution or 13,14-dihydro-15-keto prostaglandin D_2 ($DK\text{-}PGD_2$, for determination of non-specific binding, Cayman chemical

company). Compounds and DK-PGD_2 were dissolved in DMSO and diluted in the same solvent to 100x the required final concentration. Assay buffer was added to give a final concentration of 10% DMSO (compounds were now at 10x the required final concentration) and this was the solution added to the assay plate. The assay plate was incubated at room temperature for 2 hours and counted on a Wallac Microbeta liquid scintillation counter (1 minute per well).

Compounds of formula (I) have an IC_{50} value of less than (<) 10μM. Specifically, example 2 has a $pIC_{50} = 7.1$ and example 3 has a $pIC_{50} = 6.6$.

CLAIMS

1. A compound of formula (I) or a pharmaceutically acceptable salt thereof:



(I)

in which:

X is C_{1-6}alkyl or OR^6;

Y is selected from hydrogen, halogen, CN, nitro, SO_2R^3, OR^4, SR^4, SOR^3, $SO_2NR^4R^5$, $CONR^4R^5$, NR^4R^5, $NR^6SO_2R^3$, $NR^6CO_2R^6$, NR^6COR^3, C_2-C_6 alkenyl, C_2-C_6 alkynyl, C_3-C_7 cycloalkyl or C_{1-6}alkyl, the latter four groups being optionally substituted by one or more substituents independently selected from halogen, OR^6 and NR^6R^7, $S(O)_nR^6$ where n is 0, 1 or 2;

Z is aryl or a ring A, where A is a six membered heterocyclic ring containing one or more nitrogen atoms or may be a 6,6 or 6,5 fused bicycle containing one or more O, N, S atoms, the aryl or A rings all being optionally substituted by one or more substituents independently selected from from hydrogen, halogen, CN, OH, SH, nitro, CO_2R^6, SO_2R^9, OR^9, SR^9, SOR^9, $SO_2NR^{10}R^{11}$, $CONR^{10}R^{11}$, $NR^{10}R^{11}$, $NHSO_2R^9$, $NR^9SO_2R^9$, $NR^6CO_2R^6$, $NHCOR^9$, NR^9COR^9, aryl, heteroaryl, C_2-C_6 alkenyl, C_2-C_6 alkynyl, C_3-C_7 cycloalkyl or C_{1-6}alkyl, the latter four groups being optionally substituted by one or more substituents independently selected from halogen, C_3-C_7 cycloalkyl, OR^6, NR^6R^7, $S(O)_nR^6$ (where n is 0, 1 or 2), $CONR^6R^7$, NR^6COR^7, $SO_2NR^6R^7$ and $NR^6SO_2R^7$;

R^1 and R^2 independently represent a hydrogen atom, C_2-C_6 alkenyl, C_2-C_6 alkynyl, C_3-C_7 cycloalkyl or a C_{1-6}alkyl group, the latter four groups being optionally substituted by one

or more substituents independently selected from halogen, C_3-C_7 cycloalkyl, NR^6R^7, OR^6, $S(O)_nR^6$ (where n is 0, 1 or 2);

or

R^1 and R^2 together can form a 3-8 membered ring optionally containing one or more atoms selected from O, S, NR^6 and itself optionally substituted by one or more C_1-C_3 alkyl or halogen;

R^3 represents C_3-C_7 cycloalkyl or C_{1-6}alkyl which may be optionally substituted by one or more substituents independently selected from halogen, C_3-C_7 cycloalkyl, OR^6 and NR^6R^7, $S(O)_nR^6$ (where n = 0,1 or 2), $CONR^6R^7$, NR^6COR^7,$SO_2NR^6R^7$ and $NR^6SO_2R^7$;

R^4 and R^5 independently represent hydrogen, C_3-C_7 cycloalkyl or C_{1-6}alkyl, the latter two groups being optionally substituted by one or more substituents independently selected from halogen, C_3-C_7 cycloalkyl, OR^6 and NR^6R^7, $S(O)_nR^6$ (where n = 0,1 or 2), $CONR^6R^7$, NR^6COR^7,$SO_2NR^6R^7$ and $NR^6SO_2R^7$;

or

R^4 and R^5 together with the nitrogen atom to which they are attached can form a 3-8 membered saturated heterocylic ring optionally containing one or more atoms selected from O, $S(O)_n$ (where n = 0,1 or 2), NR^8, and itself optionally substituted by halogen or C_{1-3} alkyl;

R^6 and R^7 independently represents a hydrogen atom or C_1-C_6 alkyl;

R^8 is hydrogen, C_{1-4} alkyl, -COC_1-C_4 alkyl, CO_2C_1-C_4alkyl or $CONR^6C_1$-C_4alkyl;

R^9 represents aryl, heteroaryl, C_3-C_7 cycloalkyl or C_{1-6}alkyl, the latter two groups may be optionally substituted by one or more substituents independently selected from halogen, C_3-C_7 cycloalkyl, aryl, heteroaryl OR^6 and NR^6R^7, $S(O)_nR^6$ (where n = 0, 1 or 2), $CONR^6R^7$, NR^6COR^7, $SO_2NR^6R^7$ and $NR^6SO_2R^7$;

R^{10} and R^{11} independently represent aryl or heteroaryl, hydrogen, C_3-C_7 cycloalkyl or

C_{1-6}alkyl, the latter two groups being optionally substituted by one or more substituents independently selected from halogen, C_3-C_7 cycloalkyl, aryl, heteroaryl, OR^6 and NR^6R^7, $S(O)_nR^6$ (where n = 0, 1 or 2), $CONR^6R^7$, NR^6COR^7, $SO_2NR^6R^7$ and $NR^6SO_2R^7$;

or

R^{10} and R^{11} together with the nitrogen atom to which they are attached can form a 3-8 membered saturated heterocylic ring optionally containing one or more atoms selected from O, $S(O)_n$ (where n = 0, 1 or 2), NR^8, and itself optionally substituted by halogen or C_1-C_3 alkyl.

2. A compound according to claim 1 in which X is C_{1-4}alkyl or C_{1-4}alkoxy.

3. A compound according to claim 1 or 2 in which Y is hydrogen.

4. A compound according to any one of claims 1 to 3 in which Z is phenyl optionally substituted by SO_2R^9.

5. A compound according to any one of claims 1 to 4 in which R^1 and R^2 are independently hydrogen or C_{1-3} alkyl.

6. A compound according to any one of claims 1 to 5 selected from:
[(5-Methylbiphenyl-2-yl)oxy]acetic acid,
{[5-Ethyl-4'-(methylsulfonyl)biphenyl-2-yl]oxy}acetic acid
{[4'-(Ethylsulfonyl)-5-methoxybiphenyl-2-yl]oxy}acetic acid
and pharmaceutically acceptable salts thereof.

7. A compound of formula (I) according to any one of claims 1 to 6 for use in therapy.

8. A method of treating a disease mediated by prostaglandin D2, which comprises administering to a patient a therapeutically effective amount of a compound of formula (I), or a pharmaceutically acceptable salt as defined in claims 1 to 6.

9. A method of treating a respiratory disease, such as asthma and rhinitis, in a patient suffering from, or at risk of, said disease, which comprises administering to the patient a

therapeutically effective amount of a compound of formula (I), or a pharmaceutically acceptable salt or solvate thereof, as defined in claims 1 to 6.

ABSTRACT

The invention relates to substituted phenoxyacetic acids as useful pharmaceutical compounds for treating respiratory disorders, pharmaceutical compositions containing them, and processes for their preparation.